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Novel compounds

INTRODUCTION

One of the modes of inhalation delivery of pharmaceutical substances is with pMDIs (pressure metered dose inhalers). These consist of a drug suspension or solution in a liquefied propellant, nowadays an HFA (hydro fluoro alkanes) or mixture of HFAs, such as HFA 227 or HFA 134a.

To form stable formulations it is often necessary to add stabilisers or solubilisers. The stabilisers can be polymers or surfactants, and help to reduce particle aggregation and phase separation in drug suspensions. The solubilisers can be organic solvents miscible with HFAs such as ethanol, and help to solubilise the drug in the HFAs. In many cases, the addition of both stabiliser and solubiliser may be necessary, when the stabilisers need a co-solvent for solubilisation for instance.

The range of excipients (stabilisers and solubilisers) that can be used to formulate HFA pMDIs is limited because of its poor solvent properties. As a consequence most of the patented inventions related to HFA pMDI formulations rely on the addition of both solubilisers and stabilisers. In this work however, the strength of this invention is that stabilisers have been found which are naturally soluble in the HFAs in quantities large enough for them to be efficient suspension stabilisers, or even to be used as solubilising agents for the drugs being delivered.

Polymeric and surfactant stabilisers impart solubility to drug suspension in HFA by absorbing to the surface of the drug particles, and thus triggering a mechanism of steric stabilisation. For the stabilisers to be efficient, they need to be soluble in the dispersing medium to a suitable level, at least in excess of 0.5 %w/w, although this limit is excipient dependent.

The mode of action of solubilisers is simpler, as these act as solvents for the drug substance. As long as they are miscible with the HFAs, drugs can be brought into solution in the HFA-solubiliser mix. In the case of cyclodextrins, their mode of action is different.

Cyclodextrins are able to form complexes with the drug molecules, and it is this complex that is solubilised in the HFAs.

BACKGROUND TO THE INVENTION

Cyclodextrins have been used extensively for the formulation of pharmaceutical dosage forms, in particular to increase the solubility of otherwise poorly soluble drugs, or to impart controlled release properties.

More rarely have cyclodextrins been used for the formulation of inhalation products in HFAs. The only example found to date is WO03/066031. Use of cyclodextrins in HFA formulations is rare because most cyclodextrins, in particular natural cylcodextrins, are insoluble in HFAs. In WO03/066031, cyclodextrins are used to stabilise drug suspensions. This however is only possible by the addition of at least one co-solvent (one hydrophilic additive, such as PEG: poly ethylene glycol), but preferably two (one hydrophilic additive and ethanol). These co-solvents solubilise the cyclodextrin, and thus make them useful as stabilisers.

The present invention has identified the correct clyclodextrins that do not require any co-solvents, and thus constitutes a major improvement to the invention of WO03/066031.

DESCRIPTION OF THE INVENTION

It has now been found that some modified cyclodextrins are naturally soluble in HFA propellants. These are partially or fully acylated α, β or γ cyclodextrins.

It has been found that the solubilised modified cyclodextrins were very good stabilisers for drug suspensions, and that due to the ability of cyclodextrin to act as complexing agents for drug molecules, they could also be used as solubilising molecules to form solution pMDIs.

In a first aspect the invention provides HFA formulations comprising a partially or fully acylated α, β or γ cyclodextrins, the formulations being suitable for pMDI's.

In preferred embodiments, the invention provides stable dispersions or solutions for the pulmonary or nasal delivery of one or more bioactive molecule, for local or systemic administration, comprising a modified cyclodextrin in a propellant or propellant mixture. The modified cylcodextrin is a partially or fully substituted α, β or γ cyclodextrin as shown on figure 1, with R' an acyl group of the general formula: R-CO-. In particular the substituting group can be taken from the following selection: Acetyl, Acryloyl, Alanyl, Aminocarbonyl, β Alanyl, aklyl Azelaoyl, Benzoyl, tert-Butoxy, Butynyl, Caproyl, Crotomoyl, Formyl, alkyl Glutaryl, Glycoloyl, Glycyl, Glyoxyloyl, Heptadecanoyl, Hydroperoxy, Hydroxyamino, Isobutynyl, Isovalenyl, Lactoyl, Lenyl, Levulinoyl, alkyl Malonyl, Mandeloyl, Methacryloyl, Myristoyl, Monanoyl, alkyl Oxalyl, Palmitoyl, alkyl Pimeloyl, Pivaloyl, Propanyl, Salicyloyl, Seryl, Sorboyl, Stearoyl, alkyl Suberoyl, alkyl Succinyl, Theronyl, Tolnoyl, Valeryl, Valyl. Preferably the acetyl group is: Formyl, Acetyl, and Propanyl.

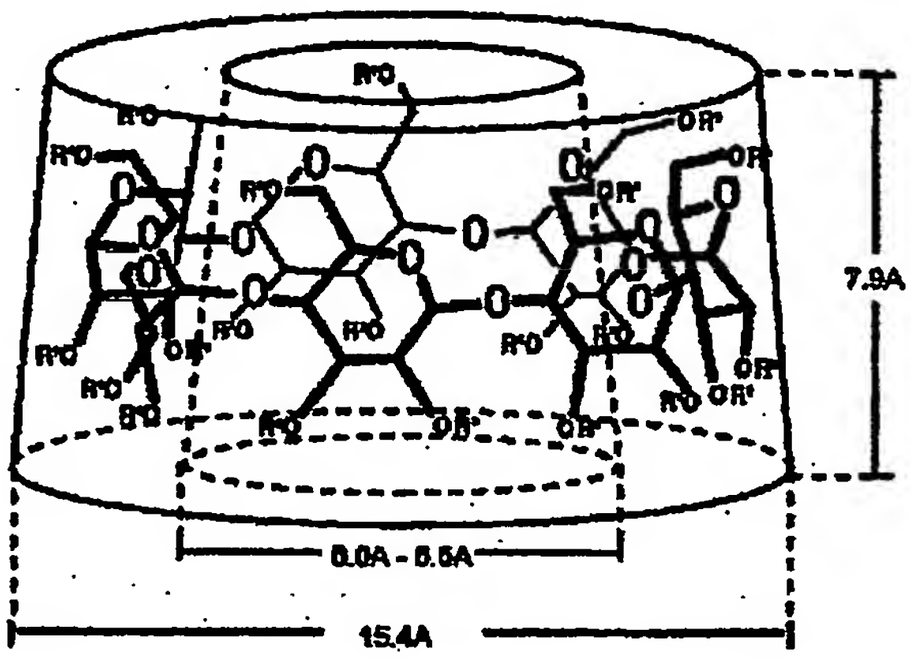


Figure 1: general structure of a modified β cylcodextrin. " R' " are the groups that can be substituted on the cyclodextrin ring with acyle functions.

Modified cyclodextrins are first solubilised in HFA 134 or HFA 227, or a mixture of both, to the required concentration levels, from 0.001%w/w to 20 %w/w, preferably from 0.001 %w/w to 10 % w/w, most preferably from 0.001 %w/w to 5 % w/w.

The active ingredient (drug) is then added to the cyclodextrin-HFA solution and filled into a pMDI canister. Alternatively, known amount of drug can be added to individual canisters and the cyclodextrin-HFA solution added to the known weight cans. The drug suspension thus formed can be homogenised by appropriate means: stirrer, ultrasonic energy etc.

The drug is any pharmaceuticaly active ingredient d used in inhalation delivery. It can be micronised if needed for targeted delivery, such as in the treatment of respiratory diseases. It may be selected from any therapeutic or diagnostic agent. For example it may be from the group of antiallergics, bronchodilators, bronchoconsitrictors, pulmonary lung surfactants, analgesics, antibiotics leukotrine inhibitors or antagonists, anticholinergics, mast cell inhibitors, antihistamines, antiinflammatories, antineoplastics, anaesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

In particular, the pharmacologically active agents in accordance with the present invention include glucocorticosteroids such as: budesonide, fluticasone (e.g. as propionate ester), mometasone (e.g. as furoate ester), beclomethasone (e.g. as 17-propionate or 17,21-dipropionate esters), ciclesonide, triamcinolone (e.g. as acetonide), flunisolide, zoticasone, flumoxonide, rofleponide, butixocort (e.g. as propionate ester), prednisolone, prednisone, tipredane, steroid esters according to WO 2002/12265, WO 2002/12266 and WO 2002/88167 (I) e.g. 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester and 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester, steroid esters according to DE 4129535 (II) and the like. Long-acting $\beta_2$agonists, without limitation, include: salmeterol, formoterol, bambuterol, TA 2005 (chemically identified as 2(1H)-Quinolone, 8-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-phenyl)-1-methylethyl]amino]ethyl]-monohydrochloride, [R-

(R*,R*)] also identified by Chemical Abstract Service Registry Number 137888-11-0 and disclosed in U.S. Patent No 4.579.854, formanilide derivatives (III) e.g. 3-(4-{[6-({(2R)-2-[3-(formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)hexyl]oxy}-butyl)benzenesulfonamide as disclosed in WO 2002/76933, benzenesulfonamide derivatives (IV) e.g. 3-(4-{[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)-hexyl]oxy}butyl)benzenesulfonamide as disclosed in WO 2002/88167 and the like. Several of these compounds could be administered in the form of pharmacologically acceptable esters, salts, solvates, such as hydrates, or solvates of such esters or salts, if any. Both racemic mixtures as well as one or more optical isomers of the above compounds are within the scope of the invention.

The preferred pharmacologically active glucocorticosteroid agents for use in accordance with the present invention include mometasone furoate, ciclesonide, zoticasone, flumoxonide, steroids from WO 2002/88167 e.g. 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester and 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid S-fluoromethyl ester, steroids from DE 4129535, fluticasone propionate and budesonide, and even more preferred is budesonide. The preferred pharmacologically active long-acting β_2-agonist is salmeterol xinafoate, formanilide derivatives (III), benzenesulfonamide derivatives (IV) and formoterol (e.g. as fumarate dihydrate) and even more preferred is formoterol fumarate dihydrate.

Combinations of pharmacologicaly active ingredients include fluticasone propionate/salmeterol xinafoate, ciclesonide/formoterol fumarate dihydrate, mometasone furoate/formoterol fumarate dihydrate, fluticasone propionate/formoterol fumarate dihydrate, and budesonide/formoterol fumarate dihydrate.

Other preferred combinations include steroids from WO 2002/88167 /formanilide derivatives from WO 2002/76933, steroids from WO 2002/88167/benzenesulfonamide derivatives from WO 2002/88167, steroids from DE 4129535/formoterol fumarate dihydrate, zoticasone/benzenesulfonamide derivatives from WO 2002/88167 and zoticasone/formanilide derivative.

A most preferred combination is budesonide/formoterol fumarate dihydrate.

A second aspect of the invention concerns the formation of drug – cyclodextrin complexes. The drug and the cylcodextrin are first solubilised in a common solvent, such as chloroform. The solution is allowed to equilibrate over a couple of days. When the complex is formed, it is extracted by for example spray drying or supercrtitical fluid extraction, such as CO_2 The solid formed is then solubilised in the HFA, or mixture thereof by virtue of the solubility of the modified cylcodextrin.

EXAMPLES

Solubility of peracetylated cyclodextrins in HFAs

The solubility of peracetylated cyclodextrins (α, β and γ) in HFA was assessed visually in clear PET vials crimped with a continuous pMDI valve. Known amounts of cyclodextrins were weighed into the PET vials. Continuous valves were then crimped on the vial, and HFAs were then added under pressure to the required amount. The samples were left to equilibrate over one week and were visually inspected. The solubility of the modified cyclodextrin was then evaluated by discriminating between samples that were clear by opposition to those samples that still had solid particles in suspension.

Following this method, the solubility of peracetyaled α cyclodextrin in HFA 227 was shown to lie between 0.1 %w/w and 1 %w/w. Its solubility in HFA 134a was shown to be above 1 %w/w.

The solubility of peracetyaled β cyclodextrin in HFA 227 was shown to lie between 1 %w/w and 2 %w/w. Its solubility in HFA 134a was shown to be between 3 %w/w and 4 %w/w.

The solubility of peracetyaled γ cyclodextrin in HFA 227 was shown to be above 1 %w/w. Its solubility in HFA 134a was shown to be above 1 %w/w.

For reference the corresponding natural cyclodextrins are insoluble in both propellants.

Peracetylated β cyclodextrin was chosen to exemplify the invention.

Efficacy of peracetylated β cyclodextrin as a suspension stabiliser

The efficacy of per acetylated β cyclodextrin as an HFA drug suspension stabiliser was tested with a selection of drug compounds.

First reference samples of pure drugs in HFAs were prepared. Then the same samples were prepared with a saturated amount of peracetylated β cyclodextrin.

The reference samples (pure drug)were prepared by weighing the drug in a PET vial. A valve was then crimped on the vial and propellant added under pressure. The vial was then sonicated for at least 15 minutes and left to equilibrate for one week.

The drug –cyclodextrin samples were prepared by weighing a known amount of drug in a PET vial. The vial was then crimped with a continuous valve. The solution of peracetylated β cyclodextrin was prepared thus: a large amount of cyclodextrin was placed in large metallic can, this was crimped and filled with the propellants. This can was left to equilibrate for at least a week. When equilibration was assumed to be reached, the saturated cyclodextrin solution was filtered into the PET vials containing the know drug amounts through a 0.2 μm PTFE filter. This way the maximum amount of soluble cyclodextrin was used in the drug suspensions. The concentration of drugs in the vials was then calculated through accurate recording of the weights added.

The phase separation phenomenon present in both samples (pure drug and with the cyclodextrin) was then recorded photographically.

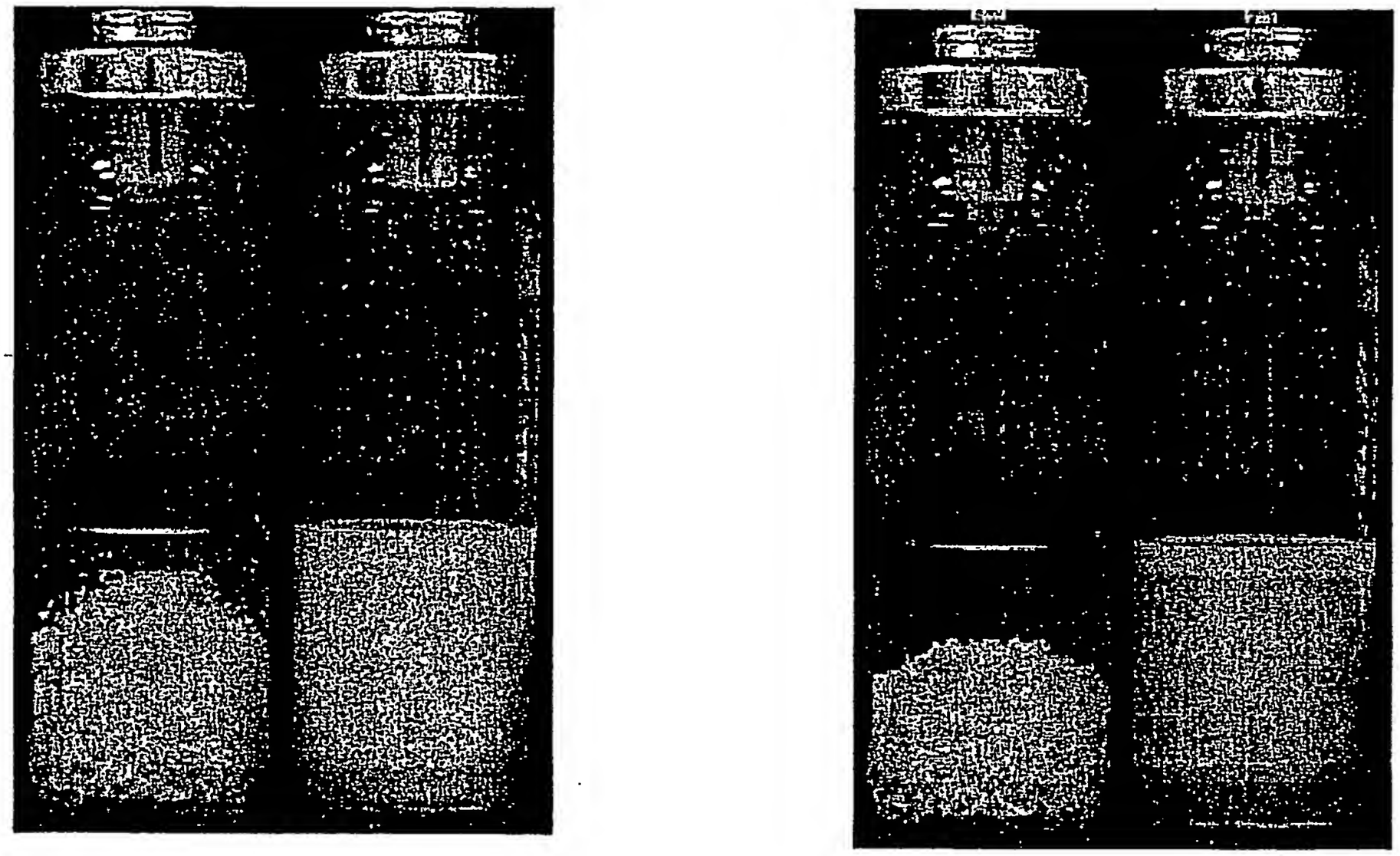
Experimental

TERBUTALINE SULPHATE

Samples in HFA 227

Left sample on figure 2: terbutaline sulphate (C= 1.03 %w/w) in HFA 227.

Right sample on figure 2: terbutaline sulphate (C= 0.97 %w/w) in saturated solution of peracetylated β cyclodextrin in HFA 227.



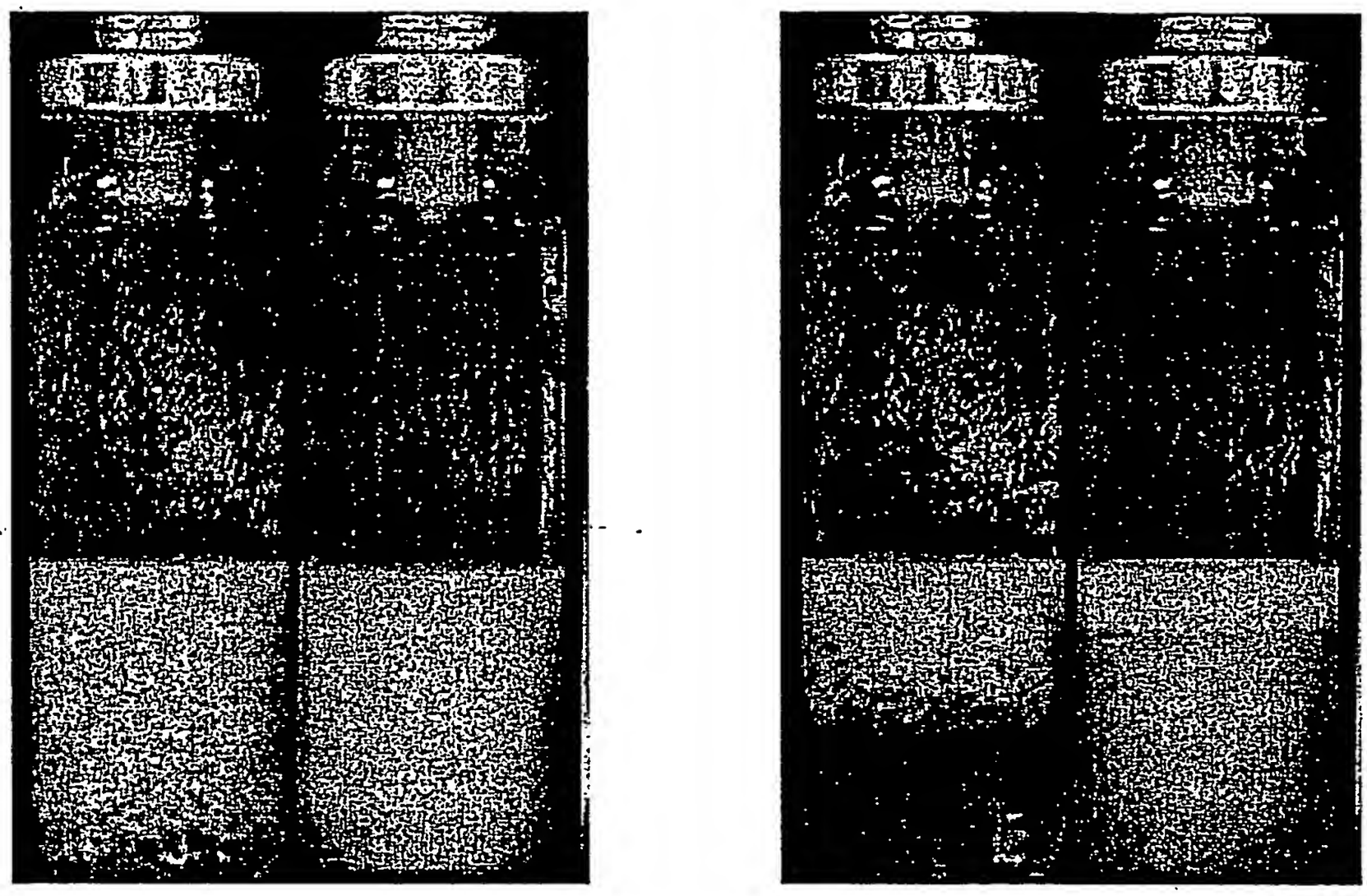
t= 10 sec after shaking t= 5 min 23 sec after shaking

Figure 2: pMDI suspensions of terbutaline sulphate in HFA 227, with (right can) and without (left can) peracetylated β cyclodextrin.

Samples in HFA 134a

Left sample on figure 3: terbutaline sulphate (C= 1.16 %w/w) in HFA 134a.

Right sample on figure 3: terbutaline sulphate (C= 1.18 %w/w) in saturated solution of peracetylated β cyclodextrin in HFA 134a.



t= 5 sec after shaking

t= 5 min 43 sec after shaking

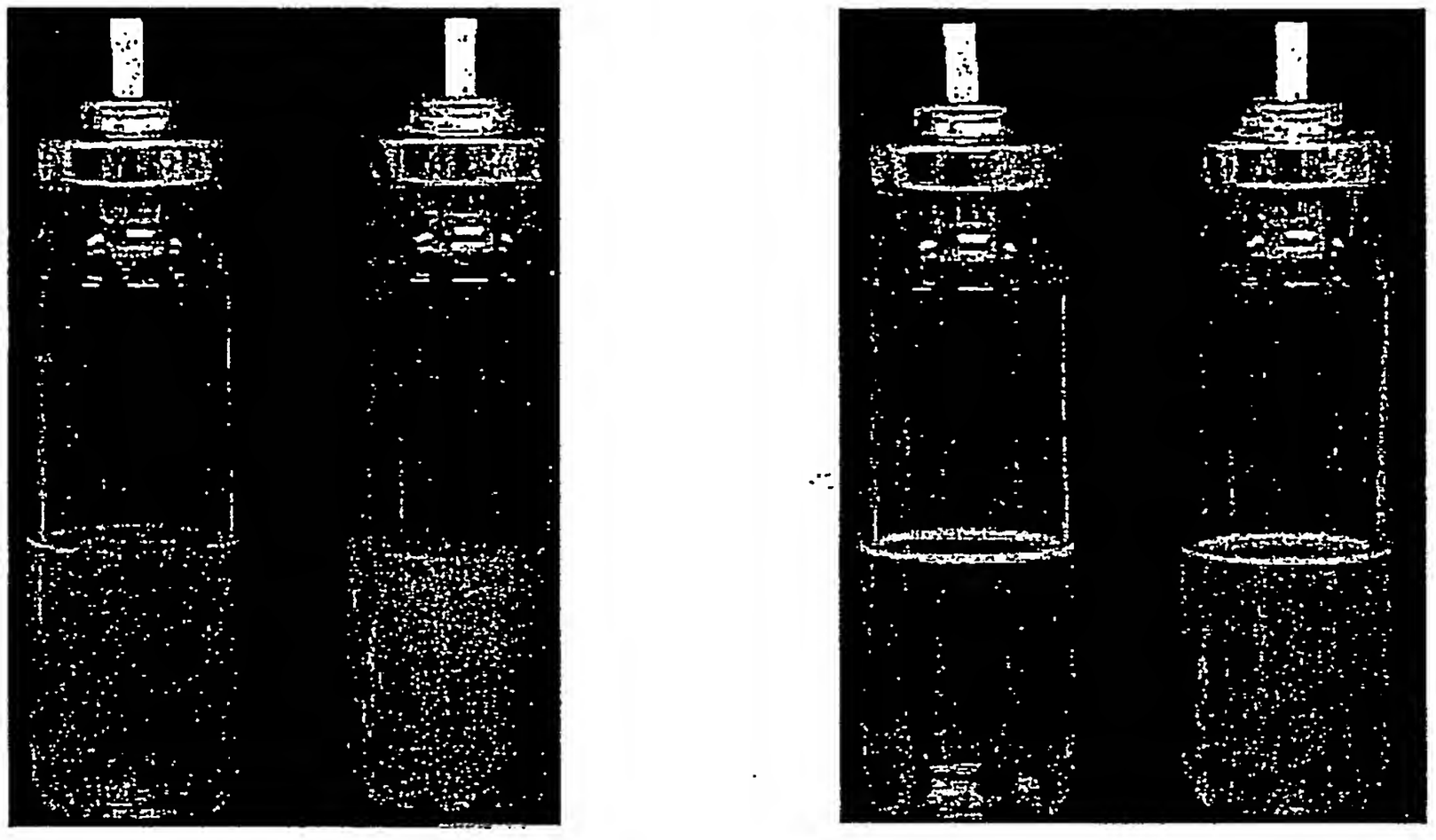
Figure 3: pMDI suspensions of terbutaline sulphate in HFA 134a, with (right can) and without (left can) peracetylated β cyclodextrin.

SALBUTAMOL BASE

Samples in HFA 227

Left sample on figure 4: salbutamol base (C= 0.1 %w/w) in HFA 227.

Right sample on figure 4: salbutamol base (C= 0.11 %w/w) in saturated solution of peracetylated β cyclodextrin in HFA 227.



t= 5 sec after shaking

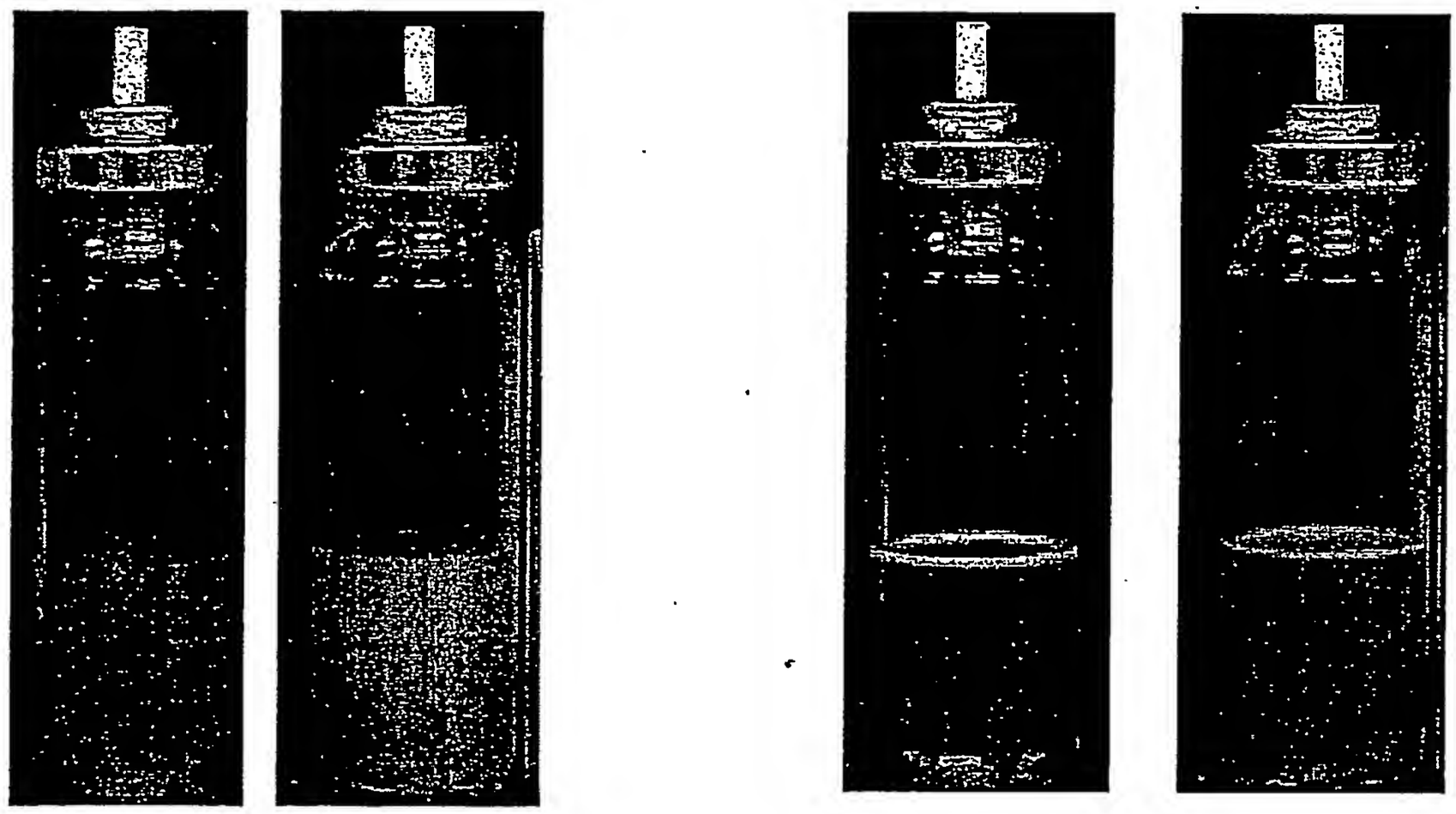
t= 19 min 33 sec after shaking

Figure 4: pMDI suspensions of salbutamol base in HFA 227, with (right can) and without (left can) peracetylated β cyclodextrin.

Samples in HFA 134a

Left sample on figure 5: salbutamol base (C= 0.13 %w/w) in HFA 134a.

Right sample on figure 5: salbutamol base (C= 0.11 %w/w) in saturated solution of peracetylated β cyclodextrin in HFA 134a.



t= 8 sec after shaking t= 15 min 50 sec after shaking

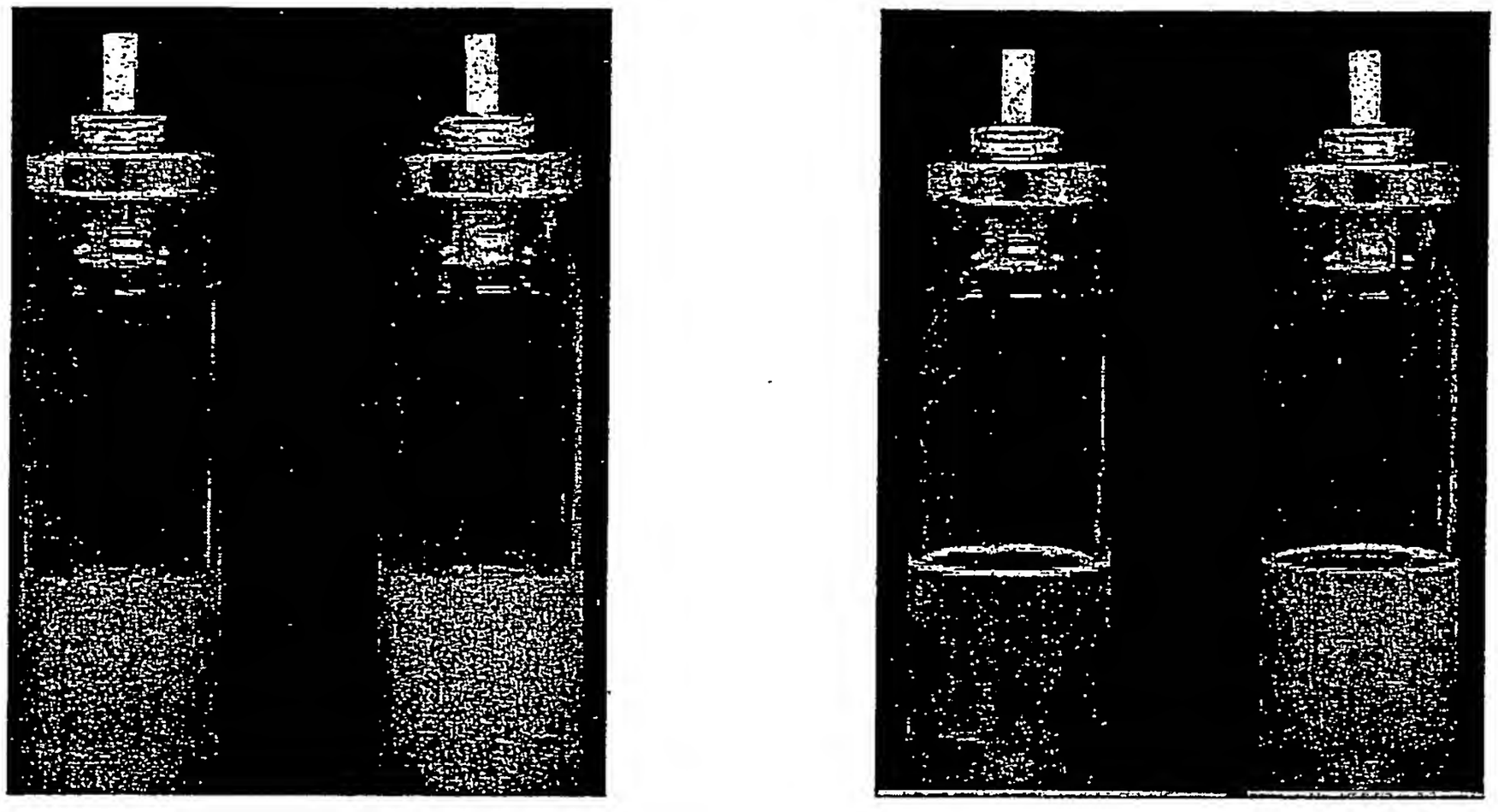
Figure 5: pMDI suspensions of salbutamol base in HFA 134a, with (right can) and without (left can) peracetylated β cyclodextrin.

SALBUTAMOL SULPHATE

Samples in HFA 227

Left sample on figure 6: salbutamol sulphate (C= 0.11 %w/w) in HFA 227.

Right sample on figure 6: salbutamol sulphate (C= 0.12 %w/w) in saturated solution of peracetylated β cyclodextrin in HFA 227.



t= 3 sec after shaking

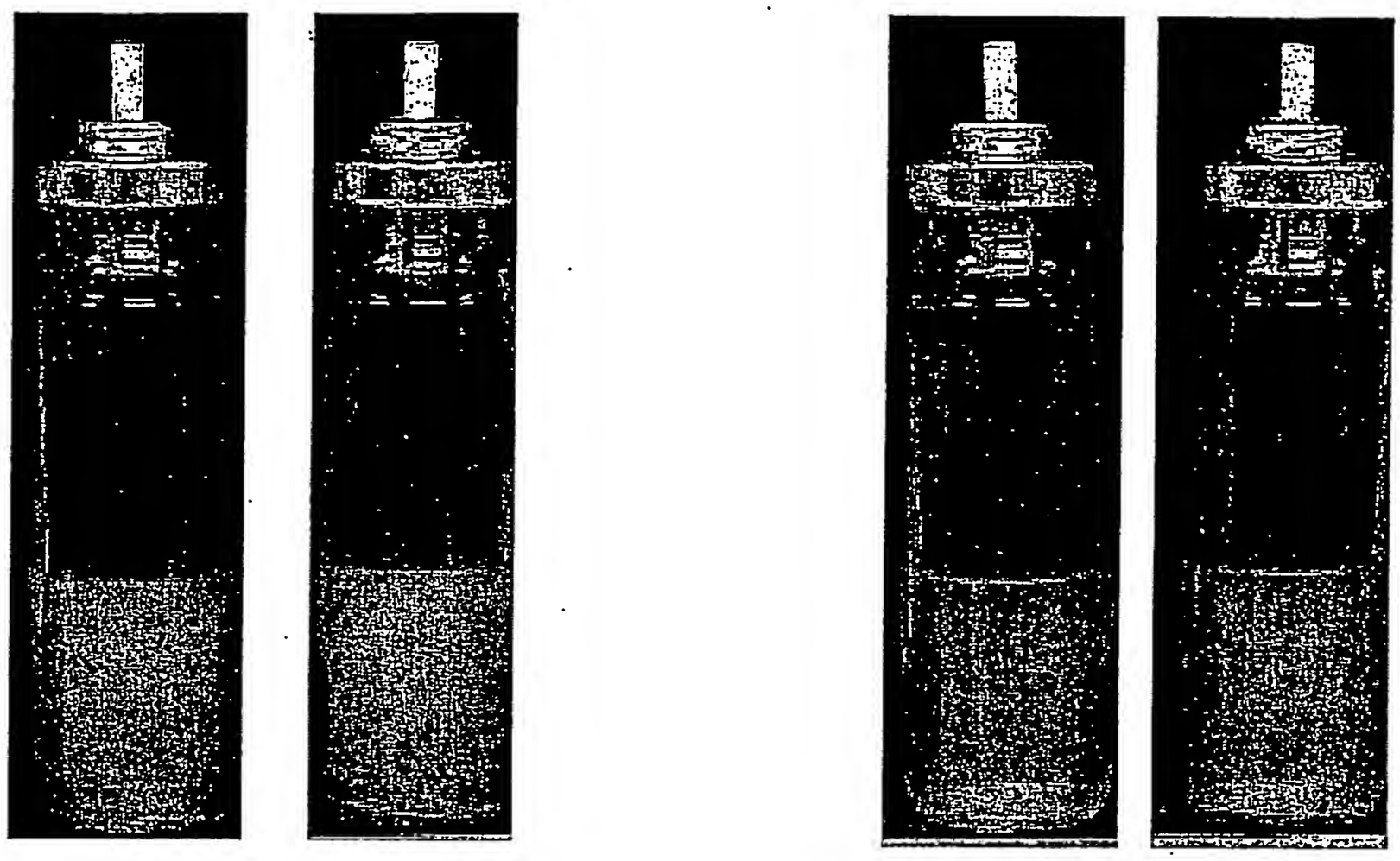
t= 14 min 24 sec after shaking

Figure 6: pMDI suspensions of salbutamol sulphate in HFA 227, with (right can) and without (left can) peracetylated β cyclodextrin.

Samples in HFA 134a

Left sample on figure 7: salbutamol sulphate (C= 0.14 %w/w) in HFA 134a.

Right sample on figure 7: salbutamol sulphate (C= 0.11 %w/w) in saturated solution of peracetylated β cyclodextrin in HFA 134a.



t= 8 sec after shaking

t= 15 min 3 sec after shaking

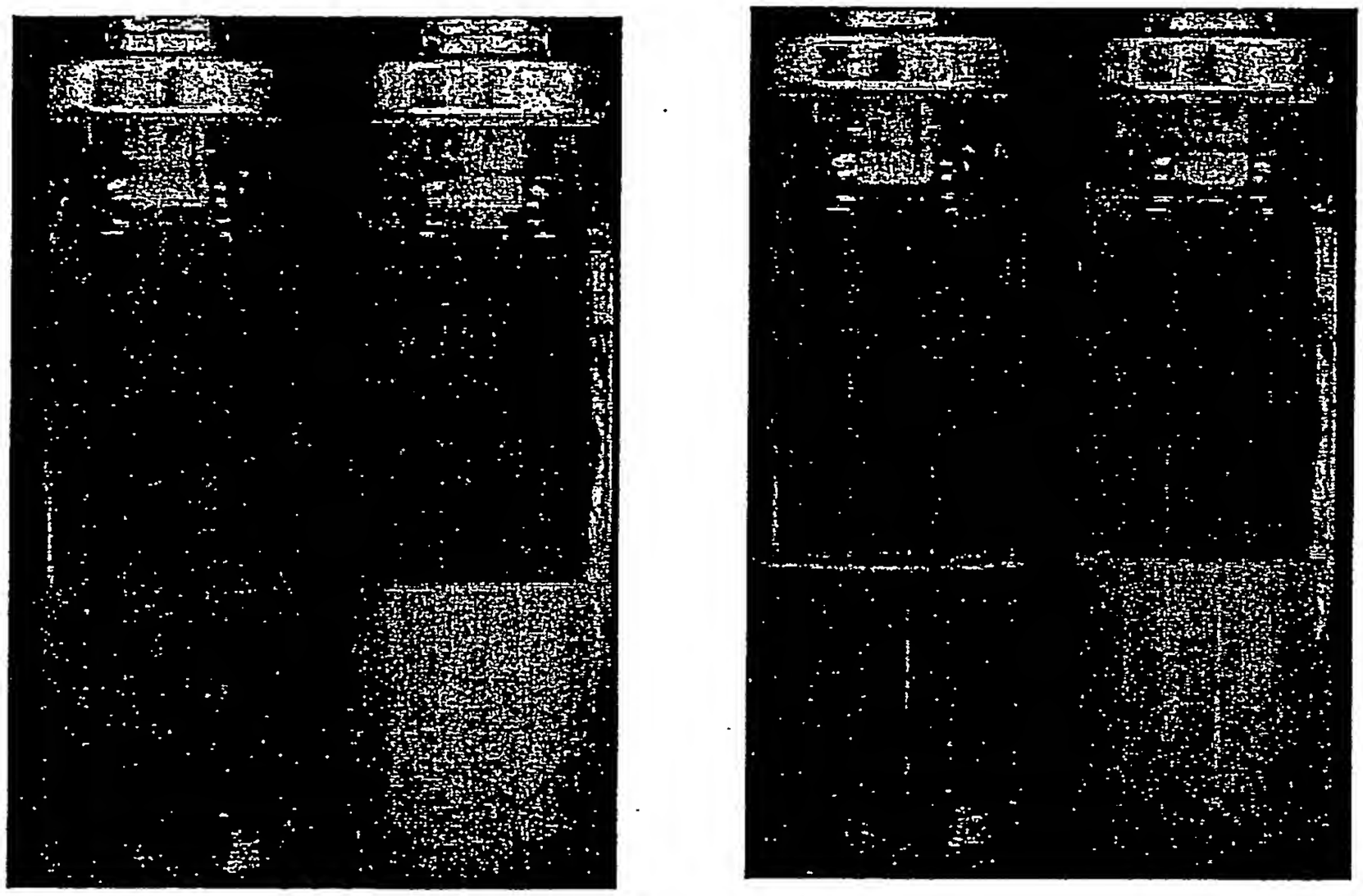
Figure 7: pMDI suspensions of salbutamol sulphate in HFA 134a, with (right can) and without (left can) peracetylated β cyclodextrin.

FORMOTEROL FUMARATE DIHYDRATE

Samples in HFA 227

Left sample on figure 8: Formoterol fumarate dihydrate (C= 0.017 %w/w) in HFA 227.

Right sample on figure 8: Formoterol fumarate dihydrate (C= 0.014 %w/w) in saturated solution of peracetylated β cyclodextrin in HFA 227.



t= 3 sec after shaking

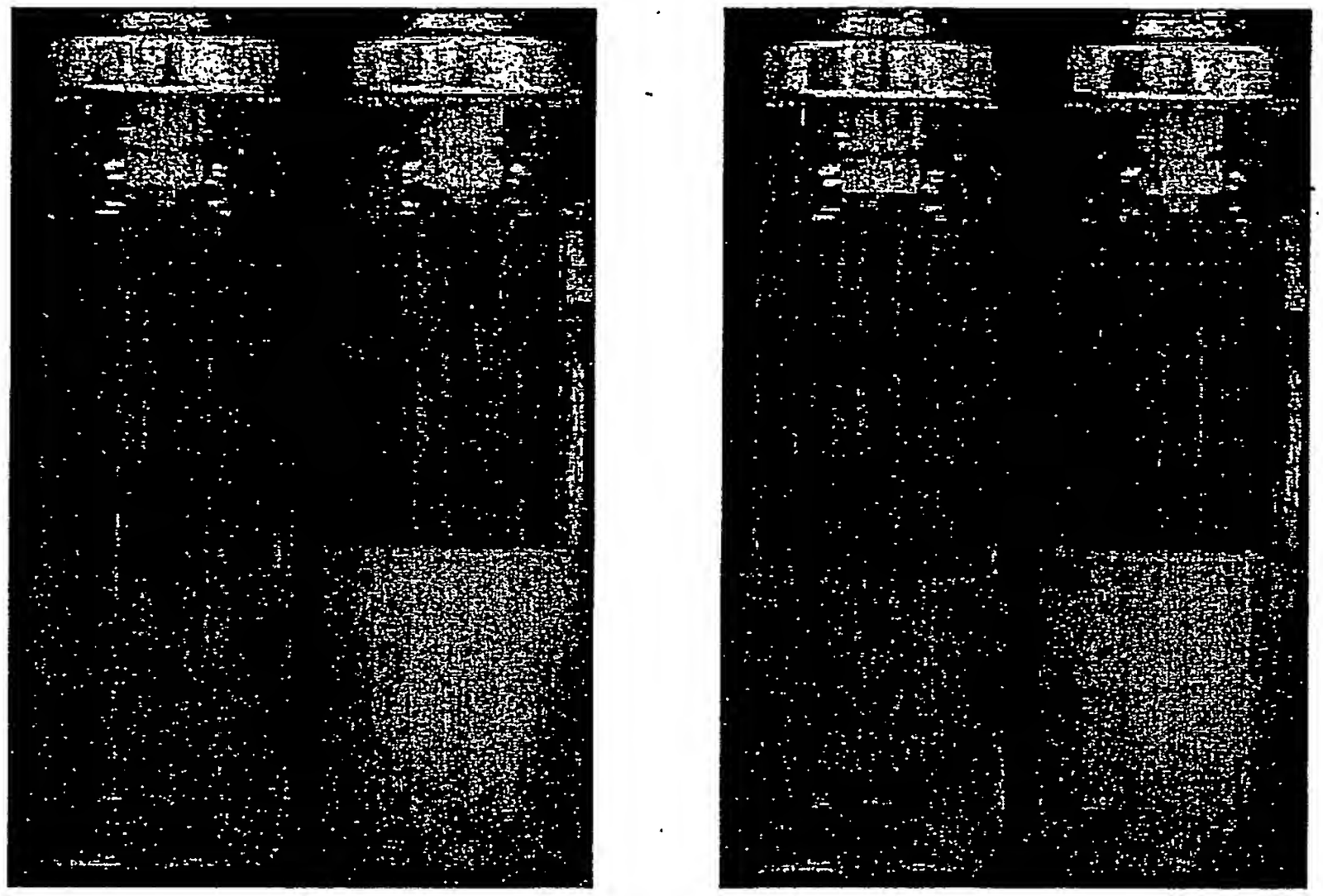
t= 8 min 3 sec after shaking

Figure 8: pMDI suspensions of formoterol fumarate dihydrate in HFA 227, with (right can) and without (left can) peracetylated β cyclodextrin.

Samples in HFA 134a

Left sample on figure 9: Formoterol fumarate dihydrate (C= 0.021 %w/w) in HFA 134a.

Right sample on figure 9: Formoterol fumarate dihydrate (C= 0.019 %w/w) in saturated solution of peracetylated β cyclodextrin in HFA 134a.



t= 3 sec after shaking

t= 5 min 10 sec after shaking

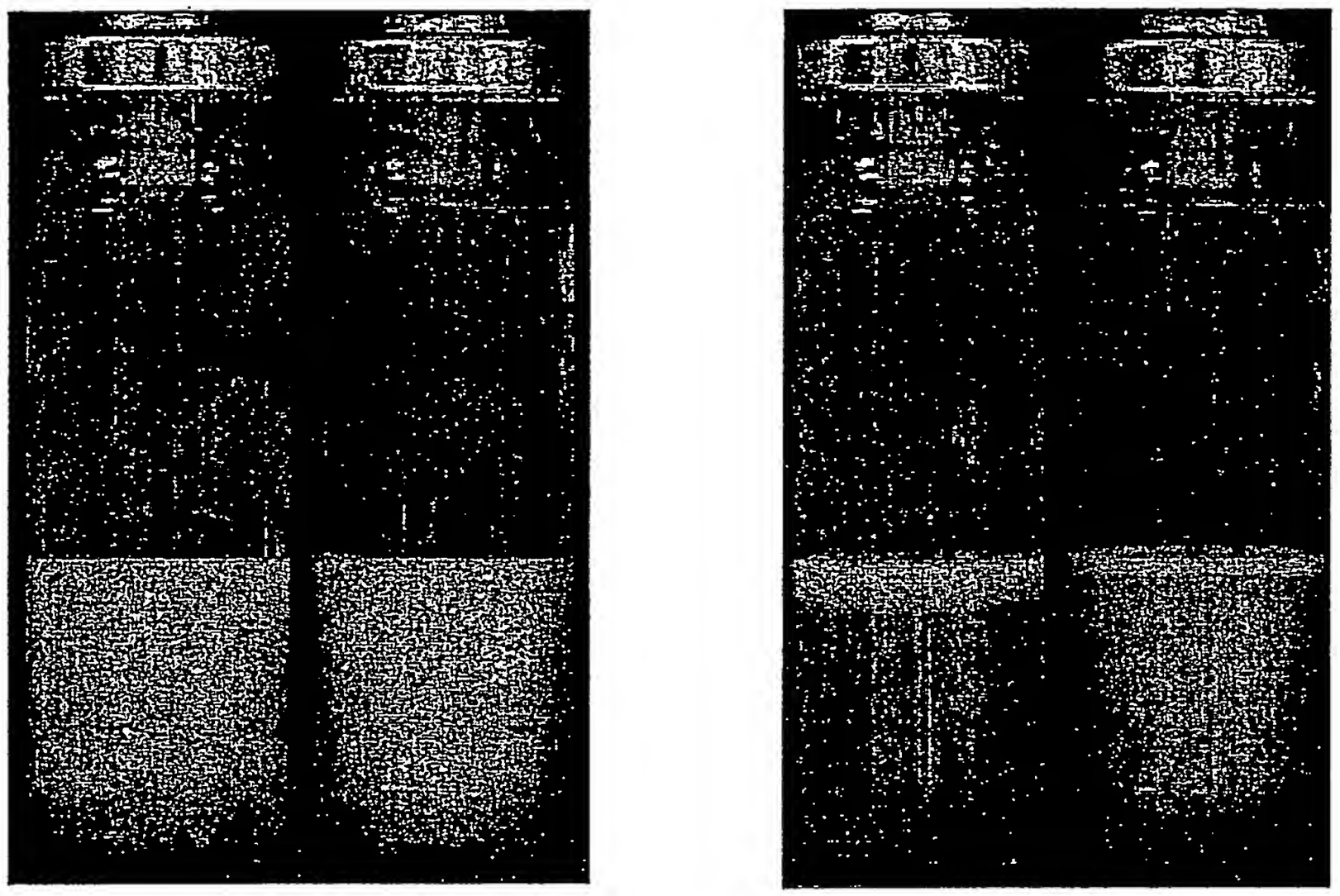
Figure 9: pMDI suspensions of formoterol fumarate dihydrate in HFA 134a, with (right can) and without (left can) peracetylated β cyclodextrin.

BUDESONIDE

Samples in HFA 227

Left sample on figure 10: Budesonide (C= 0.27 %w/w) in HFA 227.

Right sample on figure 10: Budesonide (C= 0.27 %w/w) in saturated solution of peracetylated β cyclodextrin in HFA 227.



t= 3 sec after shaking

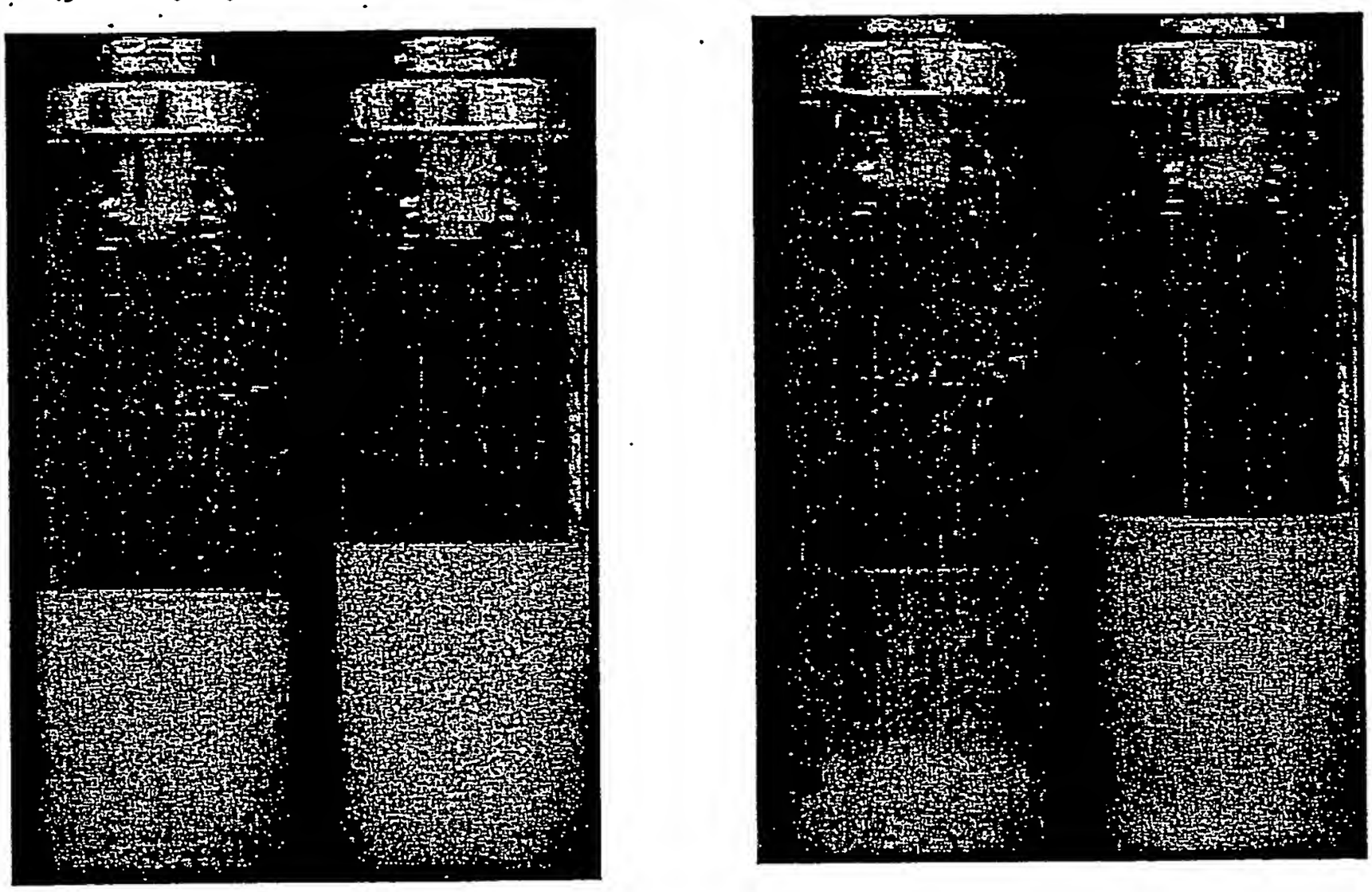
t= 5 min 1 sec after shaking

Figure 10: pMDI suspensions of Budesonide in HFA 227, with (right can) and without (left can) peracetylated β cyclodextrin.

Samples in HFA 134a

Left sample on figure 11: Budesonide (C= 0.32 %w/w) in HFA 134a.

Right sample on figure 11: Budesonide (C= 0.25 %w/w) in saturated solution of peracetylated β cyclodextrin in HFA 134a.



t= 3 sec after shaking

t= 5 min 28 sec after shaking

Figure 11: pMDI suspensions of budesonide in HFA 134a, with (right can) and without (left can) peracetylated β cyclodextrin.

Conclusions

Figures 2 to 11 show that the addition of an acylated cyclodextrin to an HFA pMDI suspension improves the suspension properties dramatically. In particular it helps to form a finely dispersed suspensions, showing little to no device adhesion. These suspensions phase separate (i.e. cream or sediment, and agglomerate) at a much lower rate than cyclodextrin fee suspensions, and are easily re-dispersible. Further more no sign of agglomeration is visible on storage.

Claims

1. An HFA drug formulation comprising a partially or fully acylated α, β or γ cyclodextrin.

2. A formulation according to claim 1 in which the HFA is HFA 134a, 227 or a mixture thereof.

3. A formulation according to claim 1 or 2 in the form of a solution.

4. A formulation according to claim 1 or 2 in the form of a suspension.

5. A formulation according to any one of claims 1 to 4 in which the cyclodextrin is acylated with one or more groups selected from Acetyl, Acryloyl, Alanyl, Aminocarbonyl, β Alanyl, aklyl Azelaoyl, Benzoyl, tert-Butoxy, Butynyl, Caproyl, Crotomoyl, Formyl, alkyl Glutaryl, Glycoloyl, Glycyl, Glyoxyloyl, Heptadecanoyl, Hydroperoxy, Hydroxyamino, Isobutynyl, Isovalenyl, Lactoyl, Lenyl, Levulinoyl, alkyl Malonyl, Mandeloyl, Methacryloyl, Myristoyl, Monanoyl, alkyl Oxalyl, Palmitoyl, alkyl Pimeloyl, Pivaloyl, Propanyl, Salicyloyl, Seryl, Sorboyl, Stearoyl, alkyl Suberoyl, alkyl Succinyl, Theronyl, Tolnoyl, Valeryl or Valyl.

6. A formulation according to any one of claims 1 to 5 in which the drug is fluticasone propionate, beclomethasone dipropionate, flunisolide, budesonide, tripedane, cortisone, prednisone, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, sabutamol, albuterol, salmeterol, terbutaline and combinations thereof.

7. A formulation according to any one of claims 1 to 5 in which the drugs are budesonide and formoterol fumarate dihydrate.

8. A formulation according to any one of claims 1 to 7 for the treatment or prophylaxis of a respiratory disease.

9. A formulation according to any one of claims 1 to 7 for the treatment or prophylaxis of asthma or COPD..

10. A method of treating a respiratory disease which comprised administering to a patient a therapeutically effective amount of a formulation according to any one of claims 1 to 7.

Abstract

Partially and fully acylated cyclodextrins have been found to be soluble in HFA propellants, and therefore can be used to formulate stable HFA pMDIs both as suspensions and solutions.

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